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PATENT SPECIFICATION (11) 1343036

1343036

(21) Application No. 9880/71 (22) Filed 19 April 1971
(31) Convention Application No. 1132 (32) Filed 20 April 1970 in
(33) Hungary (HU)
(44) Complete Specification published 9 Jan. 1974
(51) International Classification C07D 31/24 A61K 27/00
(52) Index at acceptance
C2C 173—197—288 175—270—276 213 215 220 226 22Y 246 247 250 251 25Y 28X 29X 29Y 30Y 345 346 351 352 360 363 364 366 367 368 36Y 388 624 635 701 709 718 721 761 763 790 79Y MV TP

(19)

(54) PYRIDYL METHOXYAMINES

(71) We, GYOGYSZERKUTATO INTEZET, a Hungarian Body Corporate of Szabadsagharcosok utja 47—49, Budapest IV, Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to pyridyl-methoxyamines and their salts. Furthermore the invention relates to a process for preparing these compounds.

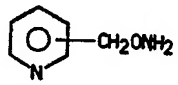
It is known that histamine exerts a decisive action on physiological and pathophysiological processes. The formation of histamine in the living organism depends on functioning of the histidine-decarboxylase enzyme (S. M. Rapoport: Medizinische Biochemie, 3rd Ed., p. 465/1965/). Certain substituted benzyloxyamines display an inhibiting effect on the function of the histidine-decarboxylase enzyme (E. L. Schumann et al., J. Med. Chem. *7*, 329/1964/). One of the effective substances of this group of compounds is 3 - hydroxy - 4 - bromobenzyloxyamine (R. J. Levine et al., Biochem. Pharmacol. *14*, 139/1965/).

A general method for the synthesis of benzyloxyamines consists in the reaction of a substituted benzyl halide with an N-protected hydroxylamine derivative (benzohydroxamic acid, N-hydroxyurethane, N-hydroxyphthalimide) and in the subsequent cleavage of the protecting group (A. O. Ilvespää and A. Marxer, Chimia *18*, 1/1964/).

Furthermore, pyridyl - 4 - methoxyamine is known from the literature (V. Markova et al., Zhurnal Obshchey Himii 3, 1207(1967/); it has been prepared for antituberculotic purposes by reacting ethyl hydroximinoacetate with 4 - chloromethylpyridine and treating the obtained ethyl - (pyridyl - 4 - methyl) - oximinoacetate with an ethereal solution of gaseous hydrogen chloride. According to the cited paper the authors obtained ethyl hydroximinoacetate with a yield of 20% and prepared therefrom pyridyl - 4 - methoxyamine with a yield of 21%.

We have now found that pyridyl - 2 - methoxyamine and pyridyl - 3 - methoxyamine exert a significant inhibiting action on histidine - decarboxylase and 5 - hydroxytryptophondecarboxylase. Toxicity of the compounds is low, a property being very important from the viewpoint of therapeutic use.

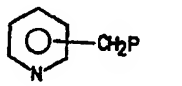
Accordingly the invention provides pyridyl-2 - methoxyamine and pyridyl - 3 - methoxyamine having the following general formula



(I)

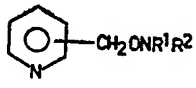
and their pharmaceutically acceptable acid addition salts.

According to the invention, these novel compounds can be obtained by reacting a substance of general formula II



(II)

wherein P represents a chlorine or bromine atom, with a hydroxylamine derivative of general formula R^1R^2NOH, wherein R^1 represents a hydrogen atom when R^2 is a carboethoxy group or R^1 and R^2 together represent a phthaloyl, isopropylidene or alpha-hydroxybenzylidene group, respectively, and subjecting the obtained compound of general formula III



(III)

wherein R^1 and R^2 have the same meanings as above, to hydrazinolysis, when R^1 and R^2 together represent a phthaloyl group, or to hydrolysis in other cases, and converting, if desired, the pyridyl-methoxyamine thus-obtained to its pharmaceutically acceptable acid addition salts.

The halomethyl-pyridines of general formula II can be prepared by known methods. For example, 3 - chloromethyl - pyridine may be obtained by reacting 3 - hydroxymethyl - pyridine with thionyl chloride (Chem. Listy *45*, 451/1951/).

Compounds of general formula II may conveniently be converted to the novel compounds of general formula III in the following manner. In the case when R^1 and R^2 together form a phthaloyl group, a halomethyl-pyridine is brought into reaction with N-hydroxy-phthalimide, in the presence of triethylamine, in dimethylformamide or acetonitrile as solvent, preferably at a temperature of 0 to 80°C. When R^1 and R^2 represent an isopropylidene and an alpha-hydroxybenzylidene group, respectively, then the halomethyl-pyridine of general formula II is reacted with acetoxime or benzohydroxamic acid, in the presence of a suitable basic substance, e.g. sodium alkoxide, in the corresponding alcohol as solvent. The boiling point of the solvent is the favourable reaction temperature. In the case when R^1 represents a hydrogen atom and R^2 is a carboethoxy group, the halomethyl-pyridine of general formula II is reacted with N-hydroxy-urethane, in the presence of a suitable basic substance, e.g. sodium hydride or sodium alkoxide, at a temperature of 20 to 100°C. The solvent is preferably dimethylformamide when sodium hydride is used, and the appropriate alcohol when a sodium alkoxide is used.

Compounds of general formula III may be suitably transformed to compounds of general formula I in the following way. Hydrazinolysis can be successfully performed in a solvent, e.g. an alcohol, at the boiling point of the solvent. Hydrolysis can be successfully carried out by boiling a few hours in alcoholic, aqueous-alcoholic or aqueous solution. The isopropylidene protecting group is removed by acid hydrolysis, while alpha-hydroxybenzylidene and carboethoxy groups are split off by alkaline or acidic hydrolysis.

For preparing the acid addition salts, pharmaceutically acceptable non-toxic acids are used. Inorganic acids fulfilling this requirement are: hydrochloric, hydrobromic, sulphuric and phosphoric acids; suitable organic acids are e.g. p-toluenesulphonic, methanesulphonic, ethanesulphonic, maleic, fumaric, succinic, tartaric and lactic acids. The salts can be prepared by methods known per se. When the pyridyl-methoxyamine is obtained by hydrolysis of the compound of general formula III, then the solution is evaporated after hydrolysis and the remainder is recrystallized to give the salt. However, when the compound of general formula I is obtained in form of the free base, then this base is dissolved in water or in a suitable organic solvent, and a solution of the acid in the same solvent or in water is added to the above solution. If the salt is not ready to crystallize, then the solution is evaporated to dryness and the residue is recrystallized from a suitable solvent.

Substances inhibiting the histidine-decarboxylase enzyme, can be suitably used in diseases where histamine has a decisive role in developing the pathological processes.

The role of histamine is well-known in physiological and pathophysiological processes. It plays a decisive role in regulating gastric secretion, in developing allergic diseases and in inflammation processes. Formation and, in some cases, overproduction of histamine depends on the function of the histadine-decarboxylase enzyme. Inhibition of the enzyme decreases the histamine concentration in tissues and produces a lower histamine level in general. E.g. in rats, the compounds according to the invention decrease the pulmonal histamine level by 50% and the gastric histamine level by 30% when given perorally in a daily dose of 3×15 mg./kg. This action is strengthened when the treatment is multiplicated. A further advantage of pyridyl - 2 - methoxyamine consists in that it exerts no inhibition against the diaminooxydase enzyme and therefore it does not influence the catabolism of histamine in the living organism. As a result of these properties, the compounds can successfully be used in the therapy of ulcus, several inflammation and allergic states, vascular headache and mastocytoma.

The following Examples further illustrate the invention.

Example 1

Preparation of pyridyl-2-methoxyamine

Method 1

Step "A":

Acetoxime (2.92 g., 0.04 moles) is added to a sodium methoxide solution prepared from 1.84 g. (0.08 g. atom) of sodium and 40 ml. of methanol and after stirring for 10 minutes, 6.56 g. (0.04 moles) of 2-chloromethyl-pyridine hydrochloride are added. The mixture is boiled for one hour. After cooling and filtration of the precipitate, the methanolic solution is evaporated on a water bath of 70°C under vacuum. The residue is triturated with 80 ml. of dichloroethane and the mixture is extracted with 3×50 ml. of water. The organic phase is dried over ignited potassium carbonate and after removing the drying agent, the solution is evaporated under vacuum on a water bath of 70°C to give O - (2 - pyridylmethyl) - acetoxime

as an oily residue, with a yield of 3.4 g. (51.7%).

Step "B":

A mixture of 3.28 g. (0.02 moles) of the above-prepared O - (2 - pyridyl) - acetoxime and 100 ml. of 4% hydrochloric acid is boiled for one hour and then evaporated under vacuum on a water bath of 50°C. The residue is mixed with 30 ml. of isopropanol and left to stand at 0 to 4°C for several hours. The crystalline precipitate is filtered by suction and dried to give 2.4 g. (60.9%) of pyridyl - 2 - methoxyamine dihydrochloride; m.p. 170 to 173°C.

Method 2

Step "A":

A solution of 12 g. (0.109 moles) of triethyl amine and 7 ml. of dimethyl formamide is added dropwise to the mixture of 9.7 g. (0.056 moles) of N-hydroxyphthalimide, 9.7 g. (0.056 moles) of 2 - chloromethyl - pyridine hydrochloride and 25 ml. of dimethylformamide at a temperature of 0 to 5°C over 25 to 30 minutes. The mixture is stirred further for one hour and then left to stand at room temperature for 3 to 5 days. 300 ml. of water are added to the mixture and the precipitate is filtered, thoroughly washed with water and dried to yield 12.4 g. (87.4%) of N - (pyridyl - 2 - methoxy) - phthalimide; m.p. 118 to 120°C after recrystallization from ethanol.

Step "B":

A mixture of 5.08 g. (0.02 moles) of the N - (pyridyl - 2 - methoxy) - phthalimide prepared as above in Step "A", 22 ml. of ethanol and 1.4 ml. of 75.9% hydrazine hydrate (0.0208 moles) is boiled for 2 hours and then cooled and filtered. The filtrate is acidified by 50 ml. of a 10% solution of ethanolic hydrogen chloride and left to stand at 0 to 4°C for one day. The crystalline precipitate is filtered and dried to give 3.37 g. (85.6%) of pyridyl - 2 - methoxyamine dihydrochloride; m.p. 172 to 174°C.

Example 2

Preparation of pyridyl - 3 - methoxyamine

Method 1

Step "A":

To the mixture of 2.4 g. (0.1 moles) of sodium hydride and 70 ml. of dimethyl formamide, 5.25 g. (0.05 moles) of N-hydroxyurethane and subsequently 8.2 g. (0.05 moles) of 3-chloromethyl pyridine hydrochloride are added and the mixture is stirred at room temperature for 48 hours. After filtration, the solution is mixed with 200 ml. of water and extracted with 2×100 ml. of chloroform. The organic phases are combined, dried over ignited potassium carbonate and evaporated to dryness under vacuum in a water bath of 60°C to give 7.05 g. (72%) of vitreous, crude ethyl N - (pyridyl - 3 - methoxy) - carbamate.

Step "B":

A solution of 5.88 g. (0.03 moles) of ethyl N - (pyridyl - 3 - methoxy) - carbamate prepared as above in step "A", 100 ml. of methanol and 30 ml. of a 4N solution of sodium hydroxide (0.12 moles) is boiled for one hour and then evaporated at 50°C under vacuum to one-third of its original volume. After adding 20 ml. of water, extraction is performed with 5×80 ml. of chloroform. The organic phases are combined, dried over ignited potassium carbonate and evaporated under vacuum at 50°C. The oily residue is triturated with 80 ml. of a 10% solution of ethanolic hydrogen chloride and cooled in ice-water for several hours. The precipitate is filtered and dried to give 3.7 g. (52.7%) of pyridyl - 3 - methoxyamine dihydrochloride; m.p. 184 to 186°C (with decomposition) after recrystallization from aqueous methanol.

Method 2

Step "A":

A solution of 32.4 g. (0.16 moles) of triethyl amine and 25 ml. of dimethyl formamide is added dropwise to the mixture of 25.3 g. (0.154 moles) of 3-chloromethyl pyridine hydrochloride, 25 g. (0.154 moles) of N - hydroxy - phthalimide and 70 ml. of dimethyl formamide under stirring and cooling by ice, at 0 to 5°C, during 40 to 50 minutes. Thereafter, the mixture is stirred for a further hour and then left to stand at room temperature for 4 to 5 days. The precipitate is filtered, washed thoroughly with water and dried to give 31.3 g. (80%) of N - (pyridyl - 3 - methoxy) - phthalimide; m.p. 149 to 151°C after recrystallization from ethanol.

An additional amount of 6.4 g. (16%) (m.p. 148 to 151°C) of the same substance is obtained from the mother liquor after dilution with water.

Step "B":

A mixture of 25.4 g. (0.1 moles) of N - (pyridyl - 3 - methoxy) - phthalimide prepared as above in step "A", 80 ml. of ethanol and 53 g. of 75% hydrazine hydrate (0.105 moles) is boiled for 4 hours, cooled and filtered. The filtrate is evaporated under vacuum at 60°C and then 30 ml. of a 30% solution of aqueous potassium carbonate are added to the residue. The precipitated oil is extracted by 2×15 ml. of n-butanol. The butanolic extracts are combined, dried over ignited potassium carbonate and filtered. The filtrate is acidified by adding a 10% ethanolic solution of hydrogen chloride until congo blue color and cooled at 0 to 4°C for one day. The crystalline precipitate is filtered and

dried to give 15.18 g. (77%) of pyridyl-3-methoxyamine dihydrochloride; m.p. 185 to 187.5°C (with decomposition) after recrystallization from aqueous ethanol or methanol.

Method 3

Step "A":

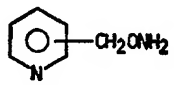
A solution of 10.8 g. (0.2 moles) of sodium methoxide in 150 ml. of methanol is added dropwise to the mixture of 25.3 g. (0.1 moles) of 3-bromomethyl pyridine hydrobromide, 50 ml. of methanol and 13.7 g. (0.1 moles) of benzohydroxamic acid at 15 to 25°C, under stirring and cooling with water. The stirring is continued for half an hour, then the mixture is boiled for one hour and subsequently evaporated at 70°C under vacuum. The residue is dissolved in the mixture of 300 ml. of water and 100 ml. of n-butanol. After separation, the aqueous phase is extracted with 2×100 ml. of n-butanol, the butanolic solutions are combined and evaporated to dryness at 70°C under vacuum to give 16.2 g. (71%) of crude O - (3 - pyridylmethyl) - benzohydroxamic acid as an oily residue.

Step "B":

A mixture of 11.4 g. (0.05 moles) of O-(3-pyridylmethyl) - benzohydroxamic acid prepared as above in step "A", 25 ml. of a 4N solution of sodium hydroxide and 75 ml. of methanol is boiled for one hour and the methanol distilled off at a bath temperature of 50°C under vacuum. After cooling, 40 ml. of water are added to the residue and the mixture is extracted with 5×80 ml. of chloroform. The organic phases are combined, dried over ignited potassium carbonate and evaporated at a bath temperature of 50°C under vacuum. The oily residue is mixed with 100 ml. of a 10% ethanolic solution of hydrogen chloride and cooled at 0 to 4°C for some days. The crystalline precipitate is filtered and dried to give 6.67 g. (68.4%) of pyridyl-3-methoxyamine dihydrochloride; m.p. 184 to 187°C (with decomposition).

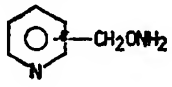
WHAT WE CLAIM IS:—

1. Pyridyl - 2 - methoxyamine and pyridyl - 3-methoxyamine having the general formula I



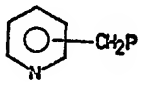
and their pharmaceutically acceptable acid addition salts.

2. A process for preparing pyridyl - 2 - methoxyamine and pyridyl-3-methoxyamine having the general formula I



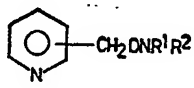
(I)

and their pharmaceutically acceptable acid addition salts, which comprises reacting a compound of general formula II



(II)

wherein P is a chlorine or a bromine atom, with a hydroxylamine derivative of general formula R^1R^2NOH, wherein R^1 is hydrogen atom when R^2 is a carboethoxy group or R^1 and R^2 together represent a phthaloyl, isopropylidene or alpha-hydroxybenzylidene group, respectively, and subjecting the obtained compound of general formula III



(III)

wherein R^1 and R^2 are as defined above, to hydrazinolysis when R^1 and R^2 together represent a phthaloyl group, or to hydrolysis, resp., in other cases, and if desired, transforming the obtained pyridyl methoxyamine to a pharmaceutically acceptable acid addition salt.

3. A process for preparing the compounds of general formula I substantially as herein described, with reference to the Examples.

4. Compounds of the general formula I as defined in claim 1, whenever prepared by a process as claimed in claim 2 or 3.

5. Pyridylmethoxyamines and acid addition salts thereof as herein described in the Examples.

6. Pharmaceutical compositions comprising as active ingredient at least one compound of general formula I as claimed in claim 1 or a physiologically acceptable acid addition salt thereof, in admixture with one or more pharmaceutical carriers and/or excipients.

7. Pharmaceutical compositions as claimed in claim 6 in the form of tablets, pills, coated pills, suppositories, capsules, solutions, emulsions, suspensions or injectable preparations.

8. Pharmaceutical compositions as claimed in claim 6 or claim 7, containing at least one other therapeutically active compound in addition to the pyridyl-methoxyamine of general formula I.

9. Pharmaceutical compositions according to any of claims 6 to 8 substantially as herein described.

10. A process for the preparation of pharmaceutical compositions as claimed in any of claims 6 to 9, which comprises admixing at

least one compound of general formula I, as claimed in claim 1, or physiologically compatible salts or quaternary ammonium derivatives thereof with one or more pharmaceutical carriers and/or excipients.

11. A process as claimed in claim 10, wherein at least one other therapeutically active compound is added to the composition.

12. Pharmaceutical compositions as herein described, whenever prepared by a process as claimed in claim 10 or claim 11.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1974.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.